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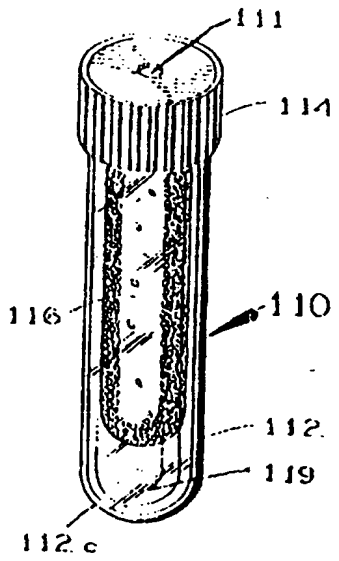
(54) Title: SAMPLE COLLECTION, DISPENSING AND RETENTION DEVICE

(57) Abstract

A multi-purpose device for sampling, collecting, recovering and storing of fluid samples, including recovery tube (112), a fluid absorbent medium comprising a cellular foam component (116), and a closure (114), which is physically coupled to the fluid absorbent element, and adapted to seal the fluid absorbent medium within the sample recovery tube. The sample recovery tube of this multi-purpose device comprises a resilient, preferably transparent, tubular member (112) having an open end, a closed end. The open end is provided with means for sealing engagement with the open end of a closure (114). In the preferred embodiments of this device, the closure is of composite construction and includes a vent or fluid channel (111) in the closed end thereof to permit access to a liquid or gas within the sample recovery tube, and is yet essentially restrictive of fluid transfer under ambient conditions.



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SAMPLE COLLECTION, DISPENSING & RETENTION DEVICE

Technical Field

This invention is directed to a device for the collection, dispensing and retention of a fluid sample, including biological fluid, such as saliva. More specifically, the instant invention is directed to a simple, yet effective device for collecting, dispensing and retention of a fluid sample for on-the-spot testing and, optionally, for sample transport and/or archival retention. In one of the preferred embodiments of this invention, chemicals and/or a test strip is integrated within the sample collection device.

Background Art

The analysis and testing of fluid samples for detection of constituents thereof generally involves initially obtaining a representative sample, and the transport of the sample to a laboratory for constituent analysis. Notable exceptions to this practice include the on-site collection and analysis of fluid samples (waste water samples for hazardous wastes) suspected of containing metals and carcinogens (qualitative testing); the breathalyzer tests administered by law enforcement for suspected drunk drivers; and the self-administered testing of blood samples for glucose which are performed on a daily basis by diabetics. In each of the instances described above, the sample is collected via some expedient and transferred to an intermediate for storage and/or contact with one or more analytical reagents.

For example, in the testing of water samples suspected of contamination by mercury a representative sample is initially obtained and placed in a suitable container and the container

either sealed for later testing, or transported to a remote laboratory for testing. As is thus apparent, the vessel containing the sample must be both conservative of the sample and preferably adapted for later dispensing thereof to avoid any contamination of the sample and of the testing environment.

In the context of the constituent analysis of a biological fluid sample, the sample is typically collected by invasive procedures (e.g., finger stick or venous puncture of sample donor for a blood sample), or as a biological waste (e.g., urine or stool specimen), depending upon the analyte of interest, and the physical condition of sample donor. The traditional methods for the invasive collection of biological fluid samples (e.g., drawing blood) is generally restricted to certain controlled and/or laboratory environments. More specifically, the securing of a sample, such as by drawing blood, necessarily involves the consent of the subject, and is limited in terms of the size of the sample that can be obtained. Moreover, such invasive procedures generally requires trained personnel to obtain the sample, and often results in a sample that is either of limited size and/or of limited stability. Alternative means of sample collection (e.g., voiding of a urine specimen) may prove to be an unacceptable option due to the unique attributes of a vital, biological fluid samples with respect to the constituents (analytes) of interest. More specifically, certain types of analytes (blood borne infections, cholesterol, triglycerides, blood alcohol, etc.) are not readily ascertainable from biological waste and, thus, there is no acceptable, alternative method for analysis other than one which employs a vital, biological fluid. Accordingly, the limitation imposed by the foregoing constraints restricts the

clinician/investigator to either a vital biological fluid (blood or saliva) or, in the case of alcohol, to a breathalyzer type test.

In the case of a breathalyzer type test, the sample obtained, by its very nature, is limited in the type of analyte that can be present therein, and is otherwise difficult to preserve and/or store. By way of contrast, a vital, biological fluid, such as saliva, is relatively easily obtained, stable, conveniently stored and contains an number of analytes of interest to both the clinician and to law enforcement. As is known, and common in saliva testing, the sample can be readily obtained by swabbing the buccal epithelial tissues in the donor's mouth for a definitive period of time to allow for the adsorption of saliva thereon.

The collection of saliva, in the latter fashion, is preferred in that it protects the individual collecting the sample from exposure thereto, and otherwise provides a relatively sterile medium in which to transfer the sample for storage, or to subject the sample to analysis.

In order to further place the subject matter of this application in perspective, a number of patent references are discussed hereinafter as representative of the state of the art.

Sangha, U.S. Patent No. 5,334,502 (the '502 patent), and the references cited therein, are fairly typical of the prior art for saliva collection, storage and testing. More specifically, the device described in the '502 patent (as illustrated in figures 7 and 8) comprises and absorbent material in the nature of a wick, which is placed in the saliva donor's mouth, allowed to remain therein until substantially saturated, and, thereafter, is removed. In the device contemplated in the '502 patent, the absorbent wick is surrounded, in part, by a capillary tube, which provides the

absorbent material with a degree of physical integrity. In the device illustrated in the '502 patent, an indicator is also provided within the device, which confirms the presence of saliva and other constituents therein. The device described in the '502 patent is purportedly useful for HIV testing and for drugs of abuse (to the extent present in the saliva).

Alternative embodiments of the saliva collection device of the '502 patent, (as illustrated in figures 1 through 6) comprises a cotton swab which is used to collect and transfer a saliva sample from the mouth of the donor to a test site (absorbent sheet or layer), which contains an indicator that can interact with the saliva and/or constituents contained therein. As is apparent, and emphasized herein, the embodiments described in the '502 patent do not provide an effective means for both isolating and dispensing the sample and, thereafter, conveniently preserving the unused portion of the sample for later use and/or testing. More specifically, the use of a cotton swab is inherently incompatible with the collection and analysis of proteinacious analytes, or protein bound analytes, in that such materials adsorb (retain, interact, etc.) the protein and thereby prevent its later release for detection and analysis. Similarly, the indiscriminate teaching of the use of plastic (col. 11, lines 13-21) as the "absorbents" for saliva collection medium, is also flawed for the same reasons given above with respect to cotton. Notwithstanding the above and additional deficiencies in the teaching in the '502 patent, the use of saliva for constituent analysis has and continues to be the source of considerable interest and investigation because of the presence of numerous analytes in saliva and its accessibility as a test specimen. Unfortunately, the deficiencies in the techniques

and devices for its collection has up to now postponed its widespread acceptance as the biological sample of choice.

Accordingly, there is, and remains, a continuing need to enhance the method by which saliva is collected from a donor and, thereafter, subjected to selective, diagnostic testing with the remainder, thereof, being stored for future use and testing (e.g., confirmation testing in the case of drugs of abuse).

It is an object of this invention to remedy the above as well as related deficiencies in the prior art.

More specifically, it is a principal object of this invention to provide a simple, yet effective device for the collection, dispensing and retention of fluids, including vital, biological fluid samples, such as saliva, which is both conservative of the sample and yet provided ease of access thereto for on-site testing and analysis.

It is another object of this invention to provide a simple, yet effective device for the collection, dispensing and retention of vital, biological fluids, such as saliva, which includes a dispensing means integral with the device.

It is yet another object of this invention to provide a simple, yet effective device for the collection, recovery, dispensing, testing and retention or storage of vital, biological fluids, such as saliva, which includes an optical window integral with the device to permit analysis of the sample within the device.

It is still yet another object of this invention to provide a simple, yet effective device for the collection, recovery, dispensing, testing and retention or storage of vital, biological fluids, such as saliva, which includes one or more components of a sample analytical system within and/or integral with the device.

A further object of the invention is to provide a sample absorbent medium suitable for use with saliva, which is fixedly attached to webbing inside of a member that can be grasped by the user, preventing swallowing of the sample absorbent medium by the donor, which member also doubles as a closure means to the sample collection tube.

A related object of the invention is to use a hydrophilic foam as the sample absorbent medium, which can be foamed in place about webbing disposed within the closure means to ensure that the sample absorbent medium cannot be separated from the closure means for safety purposes.

Additional objects of this invention include test kits and methods for on-site sample collection and testing of a vital biological fluids, specifically, test kits and methods for detection of infectious disease (HIV, HBsAG, etc.), drugs of abuse (cocaine, amphetamines, barbiturates, etc.) and therapeutic drugs (theophilin, digoxin, phenobarbital, etc.).

For ease of understanding and continuity of expression, a numerical reference has been assigned to each component part of the device of this invention based upon the function of the component in the device. Thus, a component of a specific combination having the same function as an component of another combination, is identified so that the components' function in the combination is clear even though its design may be different. Accordingly, where a component having the same common function is present in a device of more than one of the figures, the last two numbers of the assigned reference numeral will be the same in each of the figures where such common function is illustrated. For example, in applying this convention to the functional component of the sample

collection device designated as a "closure means" (which is functionally designated with the numerical reference "14"), the closure means of the collection device in each of figures 5 and 6 are, thus, labeled with the reference numerals "514" and "614", respectively.

Disclosure of the Invention

The above and related objects are achieved by providing a simple yet effective device for the collection, recovery, dispensing, testing and retention or storage of vital, biological fluid samples, such as saliva, which includes a sample collection tube (12) having an open end (12o) and a lower end, that is frequently closed, (12c); a closure means (14) having further means (13) for engagement and sealing of the open end (12o) of the sample collection tube (12); and, a sample (e.g., saliva) absorbent medium (16) fixedly attached to the inner surface (e.g., internal webbing) (22) of the closure means (14) and extending there from into the sample collection tube (12). In the preferred embodiments of this invention, the sample collection tube (12) is a tubular member having an open end (12o) and lower end, that is frequently closed, (12c); the lower end of the sample collection tube includes a reservoir (19) which allows for the segregation of the sample once it has been expressed from the fluid absorbent medium into the sample collection tube; the closure means (14) is adapted to engage and seal the open end (12o) of the sample collection tube; and, a sample absorbent medium (16) which is a bibulous member comprising a polymer foam of sufficient size and void volume to absorb a fluid sample recoverable therefrom in sufficient quantity to permit analysis and testing thereof without elaborate sample preparation or laboratory equipment and utilizing available methods and

techniques.

In the preferred embodiments of this invention, the closure means (14) includes an orifice (11) therein, which may be in the form of a vent. When the orifice is configured as a vent in the closure means (14), it is substantially restrictive of fluid transfer under ambient conditions. Thus, the vent configuration requires that a negative or positive pressure be exerted upon the fluid within the collection tube to effect the passage thereof through the vent in the closure means. In several of the alternative embodiments of this invention, the closure means (14) is of composite construction, and is comprised of an open cylinder having an internal screw thread for engagement with a complimentary thread on the collection tube (13), and a closed end (14c) defined by a snap-in accessory (15) having an orifice (11) therein. This snap-in accessory (15) can take the form of a bottle dropper, or have other functional attributes which are discussed herein. The snap-in accessories can also be used on the lower end (12c) of the collection tube as hereinafter described.

It is essential to the efficacy of the device contemplated herein that the sample absorbent medium (16) be matched to the physical and chemical properties of both the fluid sample and the analytes contained therein, in that it must be both capable of absorption and release of the sample and constituents of interest to allow for analysis thereof without any substantial interaction or adsorption thereof. In the preferred embodiments of this invention, the sample absorbent medium (16) is an open cell polymer foam (prepared from a HYPOL brand urethane pre-polymer, available from W.R. Grace & Co., Boca Raton, Florida, USA) that is substantially inert (cross-linked) and otherwise unreactive (e.g.,

non-adsorbent) toward both the fluid sample and the analytes of interest with in the fluid sample. This foam, (and other comparable materials), can be formulated, as desired, to have the requisite density and other physical properties consistent with the inherent characteristics of the absorbed fluid, and the contemplated method of sample collection and analysis. In the preferred embodiments of this invention, the physical size and shape of the absorbent foam medium (16) roughly parallels the shape of the chamber defined by the housing, and yet has a comparatively small profile (generally 50 to 60% of the collection tube).

In a number of the alternative embodiments of this invention, the sample collection tube (12) is comprised of a resilient elastomeric material and is preferably provided on the lower end (12c) thereof with functional tip (20) that can dispense the saliva if and when it is expressed from the sample absorbent medium. In one of the alternative embodiments of the invention, the lower end (20c) of the functional tip (20) can be opened and thereafter resealed. This functional tip (20) is optionally provided with one or more indices (not shown), or graduation marks, corresponding to fluid volume, (analogous to a pipette), and, thus, can be used to dispense a metered amount of fluid (saliva) by simply squeezing the housing.

In another of the alternative embodiments of this invention, either the closure means (14), and/or the functional tip (20) of the collection tube (12), can be further modified to provide a fitting (18) for mating with a syringe (50) or a fixture (32) containing an analyte sensitive element. The functional tip (20) can also include an internal pressure activated valve (21) to eliminate the need for re-sealing of the functional tip when

dispensing a sample. Another alternative embodiment includes an analyte sensitive element (80) disposed on the interior of the collection tube.

The functional tip (20) of the sample collection tube is adapted to engage a syringe (50) or a fixture (32) so as to create leak proof union of the two and thereby provide a fluid pathway from the collection tube. Thus, subsequent to, or concurrent with, expressing of the fluid sample from the fluid absorbent medium (16) (e.g., squeezing the foam) in the collection tube, it can be directly applied from the reservoir within the sample collection tube to a fixture (32) containing an analyte sensitive element or to a syringe (50) and thence to a test element without any loss or inadvertent contact with the clinician. Moreover, since only the requisite amount of sample to perform the assay is used, the balance is conserved for re-testing or simply retained within the secure environment of the collection device, thus, insuring against its cross-contamination and/or infection of unsuspecting individuals.

The volume of saliva that is collected by the fluid absorbent medium (16) is a function of both the size of the absorbent medium (16) and, of course, the time the medium is in contact with the donor. A typical saliva collector of this invention has a fluid absorbent medium (16) of sufficient size and fluid capacity to absorb and thereafter release (express) a sufficient volume of saliva (from about 100 to 200 microliters) for performance of at least one screening assay and at least one conformation assay (should that be required). As more fully se forth herein, the volume of sample contemplated for us in the solid phase immunoassays of interest will generally require at least 50, and

preferably 100, microliters.

The test kit of this invention, includes at least one analyte sensitive element and at least one sample collection device of this invention along with instructions for the performance of an analysis of the collected fluid sample. In an alternative embodiment of this test kit, one of more additional reagents can accompany the analyte sensitive element. More specifically, the preferred test kit of this invention includes a physically discrete fixture (e.g., having an analyte sensitive element), such as a test icon which is uniquely designed to mate with the foregoing sample device and thereby provide a direct and convenient means for transfer of the fluid contents from the collection device so as to permit its analysis.

Alternatively, the test kit can simply include an analyte sensitive element and/or interactive chemicals within a housing that is common to the sample absorbent medium, wherein each are maintained isolated from the other until the appropriate time for transfer of sample to the analyte sensitive element.

Brief Description of Drawings

Figure 1 is a perspective view of a preferred embodiment of a sample collection device of this invention;

Figure 2 is an exploded view of the sample collection device of figure 1, which includes a sample collection tube and composite closure means;

Figure 3A shows an enlarged exploded view of the composite closure means of figure 2A, showing internal webbing around which is foamed sample absorbent medium to render the closure means inseparable from the sample absorbent medium and wherein the closed end of the closure means comprises a snap-in accessory having an

orifice;

Figure 3B shows an enlarged view of the open end (threaded member) of the composite closure means of figure 3A;

Figure 4A shows an alternative snap-in accessory for the composite closure means of figure 2A, wherein the snap-in accessory is configured for dispensing an aliquot of sample from the collection device;

Figure 4B shows an alternative snap-in accessory for the composite closure means of figure 2A, wherein the snap-in accessory includes a fitting that is configured for mating with a fixture which can include an analyte sensitive element;

Figure 5 shows a sample collection device wherein the lower end of the collection tube includes a skirt;

Figure 6A shows a sample collection device wherein the lower end of the collection tube includes pipette tip;

Figure 6B shows a sample collection device wherein the lower end of the collection tube includes a dispensing tip having an internal pressure activated valve;

Figure 7 shows an alternative embodiment of the sample collection device of figure 5, wherein the collection tube is modified on the lower end thereof to accept a snap-in accessory of the type illustrated in figure 4B;

Figure 8 shows an exploded view, in part, of the sample collection device of figure 7;

Figure 9 shows a sample collection device of figure 8 in mating relationship with a syringe;

Figure 10 shows the sample collection device of figure 5 in incipient mating relationship with a Vacutainer-like syringe;

Figure 11 shows the sample collection device of figure 5 in

cooperative relationship with a test icon;

Figure 12 shows an alternative embodiment of the sample collection device of figure 1 wherein the sidewall of the collection tube includes a reagent coating specific for interaction with one or more constituents of the sample;

Figure 13 shows the sample collection device of figure 1 in a test kit;

Figure 14 shows the test kit of figure 13 in a workstation configuration.

Best Mode for Carrying Out the Invention

As is discussed more fully herein, the design and operation of the various components of the sample collection device all cooperate to collect a fluid sample in sufficient volume as to be representative of the environment from which it has been obtained, and, thereafter, permit dispensing of an aliquot of such fluid for constituent analysis. The device of this invention incorporates these multiple functions into a single, yet simple, design.

More specifically, the basic structure of the device (110) is illustrated in figure 1 and generally includes four (4) functional components, specifically, a sample collection tube (112), a closure means (114) for the collection tube (112), a sample absorbent foam medium (116) for collection (absorption) of the liquid sample, (e.g., a biological fluids sample such as saliva) and an orifice (111) for accessing the sample collection chamber within the device (110) so as to permit dispensing of an aliquot of the sample without removal of the closure means (114).

As illustrated in the exploded view of this sample collection device (210) set forth in figure 2, the sample absorbent foam medium (216) is integrated into the closure means (214) and the

closure means (214) itself is of composite construction. The composite nature of the closure means is further illustrated in figure 3A and 3B. More specifically, the closure means (314) includes a lower end (314c) and open end (314o) which are structural and functionally unique.

The open end (314o) of the closure means (314) is a cylindrical element having internal threads that engage similar threads (213) on the open end (212o) of the collection tube. See figure 2. Moreover, the closed end (214c, 314c) of the closure means (214, 314) is provided with a detente, (217, 317) for acceptance of a snap-in accessory (215, 315,). The snap-in accessory (215, 315) is complimentary with the recess (217, 317) in the closed end (214c, 314c) of the closure means (214, 314) so as to form a locking seal between the snap-in accessory and the recess/detente.

Alternative embodiments of this closure means snap-in accessory of figures 2 & 3 are shown in figures 4A and 4B. More specifically, the closure means snap-in accessory shown in figure 4A can take the form of a dropper bottle tip (415) and, thus, permit the dispensing of an aliquot of a recovered sample from the reservoir of the collection device onto an analyte sensitive element, or into a cuvette, for constituent analysis of the sample. Another embodiment of this invention contemplates a closure means snap-in accessory design which includes a fitting (418) adapted for mating with a fixture (432) for an analyte sensitive element that is capable of manifesting the presence of the analyte of interest, if present in the sample.

In each of the preferred embodiments of this invention, the closure means snap-in accessory (415) is designed to provide a less

than air tight seal, or have an orifice (111) that may be a vent therein, to permit the vapor and/or gas (e.g., air), that is trapped within the sample collection tube (112), to be expelled at the time of expressing the sample from the sample absorbent medium into the sample collection tube (112). Thus, in the context of this invention, the term "fluid" as used in conjunction with the term "vent" is inclusive of both liquids and gases. The vent (111) in the cap allows for both the compression of the collection tube (112) during the dispensing of the sample and its return to original shape. In each instance, the sample absorbent foam (116) remains firmly affixed to the internal structure of the closure means (114) because it was foamed in place around the webbing thereof as a safety consideration, i.e., to prevent ingestion of the sample absorbent medium (116) when placed in a donor's mouth to collect saliva, particularly if the donor is an infant or child.

As emphasized herein, the device (110) of this invention, as shown in figure 1, can be used in a variety of environments and thus its specific construction will be dictated accordingly. More specifically, where this device (110) is to be used to collect a fluid sample containing a hazardous waste, comprising a highly acidic substance, the materials selection for the components of the collection device (110) must be resistant to degradation by the sample. Similarly, where the device (110) is to used in the collection of a biological fluid, such as saliva, the materials selection for the collection tube, and the sample absorbent medium (116) must be suited to this task - inactive relative to proteins and constituents (collectively "analytes") of the sample. Moreover, where the device (110) is to be placed in contact with the donor, (e.g., in the donor's mouth), the sample absorbent

medium (116) cannot be ingested or subject to breakdown from the enzymes contained in the saliva or otherwise include any substance that can be leached from the medium (116) during the collection process, or thereafter during the dispensing of the sample from such medium. The chemical and physical properties of the sample absorbent medium (116) used in the collection of the saliva are, thus, essential to the efficacy of the device, specifically the ability to absorb and thereafter release the biological fluid to allow for the analysis of the constituents contained therein.

In the preferred embodiments of this invention, the sample absorbent medium (116) for a saliva collection device (110) of this invention is an inert (e.g., cross-linked) plastic which is prepared from a pre-polymer which is processed to produce an open cell foam having characteristics consistent with the foregoing sample collection and analysis requirements. In the preferred embodiments of this invention, the sample absorbent medium (116) is formed of a water catalyzed polyurethane pre-polymer, for the type available from Hampshire Chemical Corporation, a subsidiary of W.R. Grace, under the HYPOL trademark.

These HYPOL brand polyurethane pre-polymers can be synthesized in accordance with the materials and procedures described in U.S. Patent No. 3,903,232 (which is herein incorporated by reference in its entirety). The processing conditions and composition of the foam are geared to provide a very high adsorption density (open cell foam) and sufficient tensile strength to withstand the rigors of sample collection and thereafter the dispensing thereof by the compression of the foam so as to express the sample into the sample collection tube where it can be contacted with a analyte sensitive element or dispensed onto a test strip for analysis. Obviously

this material must also be chemically inert (relative to the sample) and devoid of any unreactive and/or labile materials which can be ingested during the process of sample collection. In one of the preferred embodiments of this invention, this foam composition can be prepared from a hydrophilic cross linked polyurethane foam by interaction of an isocyanate terminated polyethylene polyol with large amounts of an aqueous reactant. The resultant foams produced thereby can be molded to size and/or compressed. These foams are preferably a low density polyurethane foam (one to about three pounds per cubic foot) which is readily compressible to about one-fifteenth or even one twentieth its original size.

These foams can be synthesized by initially capping (terminating) a polyoxyethylene polyol with an isocyanate. In brief, this process involves reacting a polyoxyethylene polyol with a polyisocyanate in a non-oxidizing atmosphere (nitrogen), at atmospheric pressure within a temperature range from about 0°C to about 120°C for a period of time of about twenty (20) hours, depending upon the temperature and the degree of agitation of the interactive constituents. The polyisocyanates used for capping the polyoxethylene polyol include polyisothiocyanates, polyisocyanates which are PAPPI I (polyaryl polyisocyanate as defined in U.S. Patent No. 2,683,730), tolylene diisocyanate, triphenylmethane - 4,4',4", triisocyanate, benzene-1,3,5-triisocyanate, hexamethylene diisocyanate, xylene diisocyanate, chlorophenylene diisocyanate, diphenylmethane-4,4'-diisocyanate, naphthalene-1,5-diisocyanate, xylene-alpha, alpha-diisothiocyanate, 3,3'dimethyl-4,4'-biphenylene diisocyanayte, 4,4'-methylenebis (phenylisocyanate), 4,4'-sulfonylbis (phenylisocyanate), 4,4J-methylene

diorthotolylisocyanate, ethylene diisocyanate, ethylene diisothiocyanate, trimethylenediisocyanate and the like. Mixtures of any one or more of the above mentioned organic isothiocyanates or isocyanates may be used as desired. The aromatic diisocyanates and polyisocyanates or mixtures thereof which are especially suitable are those which are readily commercially available, have a high degree of reactivity and a relatively low cost.

Capping of the polyoxyethylene polyol may be accomplished using stoichiometric amounts of reactants. Desirably, however, an excess of isocyanate is used to ensure complete capping of the polyol. Thus, the ratio of isocyanate groups to the hydroxyl groups used for capping is between about 1 to about 4 isocyanate to hydroxyl, and 2 to 5, preferably about 3, isocyanate to hydroxyl molar ratio. In order to achieve an infinite cross-linked network formation on foaming, the reactive components may be formulated in one of the following examples.

First, when water is the sole reactant with the isocyanate groups leading to chain growth during the foaming process, the isocyanate capped polyoxyethylene polyol reaction product must have an average isocyanate functionality greater than 2 and up to about 6 or more depending upon the composition of the polyol and capping agent components.

Secondly, when the isocyanate capping polyoxyethylene polyol has an isocyanate functionality of only about two, then the aqueous reactant, may contain a dissolved or dispersed isocyanate-reactive cross-linking agent having an effective functionality greater than two. In this case, the reactive cross-linking agent is reacted with the capped polyoxyethylene polyol when admixed during and after the foaming process has been initiated.

Thirdly, when the isocyanate capped polyoxyethylene polyol has an isocyanate functionality of only about two, then a polyisocyanate cross-linking agent having an isocyanate functionality greater than two, may be incorporated therein, either preformed or formed in situ, and the resultant mixture may then be reacted with the aqueous reactant, optionally containing a dissolved or dispersed reactive isocyanate-reactive cross-linking agent, leading to a cross-linked, infinite network hydrophilic polyurethane foam.

In the context of this invention, the sample absorbent medium is formed by simple and well-known fabrication methods. For example, foams can be foamed for fluid sample absorbent medium of this invention, from the foregoing HYPOL like pre-polymers, utilizing techniques analogous to those described in Newman, U.S. Patent No. 4,944,947, which is incorporated by reference in its entirety. More specifically, Newman describes fabrication of a dental appliance from a HYPOL foam pre-polymer (HYPOL FHP- 2002), which is simply added to an aqueous medium at an elevated temperature (110°F, 38°C), and thereafter stirred vigorously until frothy. A given amount of this mixture is then cast into molds which have been pre-heated to 100°F, the molds clamped closed and the polymer permitted to cure (cross-link). After an abbreviated period, the molds are opened and the molds foam article is removed. Curing of the foam continues until the cross-linking reaction has gone to completion.

In the preferred embodiments of this invention the closure means (214) is initially affixed to the mold (not shown) and the sample absorbent medium (216) formed by injection of the foam into a mold through the top of the closure means (214). As the foam

expands, it fills the mold and flows onto the closure means. Sufficient foam is charged to the mold to cause the expansion thereof into the closure means (314) so as to become entrained by webbing (322) within the closure means (314) where it remains fixedly attached to the webbing upon curing.

As illustrated in figures 1 & 2, the sample collection tube (112, 212) of the collection device (110, 210) of this invention can have a simple round bottom configuration, depending upon its intended use, a flexible and resilient sidewall construction and versatility for configuration with other functional components of the invention. In another of the alternative embodiments of this invention, the sample collection tube (112) can be prepared from a relative rigid material, (e.g., thermoset plastic). In each of the embodiments of this invention, the sample collection tube (112) has an open end (112o) and a lower end, that is frequently closed, (112c). The open end (112o) is of sufficient diameter to accommodate the insertion and removal of the sample absorbent medium (116), and is further provided with external threads, or an equivalent expedient, for sealing engagement by a screw cap or comparable closure means (114).

By way of contrast, the sample collection device (510) illustrated in figure 5, comprises a skirted tube (512). As more fully illustrated in these accompanying figures (figures 5 to 8 inclusive), the lower end of the sample collection tube (512) of the collection device (510) of this invention can include various means for accessing the fluid from within the tube, and for resealing the lower end of the sample collection tube after an aliquot of the sample has been obtained.

For example, the device (610) illustrated in figure 6A, the

sample collection tube (612) is provided on the lower end (612c) thereof with a dispensing tip (620) that can be opened and released. The tip can be re-sealed by simply heating the tip until it melts or with an appropriate closure means such as a selectively removable cap (623) designed for that purpose. The inclusion of an internal pressure activated valve (621), of the type shown in figure 6B, eliminates the need for re-sealing of the dispensing tip (620). More specifically, upon exertion of pressure on the contents of the sample collection tube (612) the valve (621) is forced to open and thereby permits the flow of fluid from within the sample collection tube. In the absence of such pressure, the dispensing tip (620) remains sealed and the contents of the tube secure.

As noted above, and once again emphasized, the sample collection tube (112) of the collection device (110) of the type shown in figure 1 is preferably of a flexible side-wall construction, and transparent to allow for observation of the sample within the sample collection tube (112). Thus, once the sample has been collected on the sample absorbent medium (116) and this medium inserted in the tube, the tube is sealed with the closure means (114). In the preferred operation and use of the sample collection device of this invention, the sides of the sample collection tube are squeezed so as to compress the sample absorbent medium therein and thereby express the sample from the sample absorbent medium into a reservoir (119) provided at the lower end (112c) of the sample collection tube (112). Once the sample is expressed, the vertical orientation of the tube, and the distance between the expressed sample and the sample absorbent medium prevents the re-contact of the two with each other in the

reservoir.

Obviously, it is desirable from both a consumer and manufacturing perspective to provide one or more basic designs for the sample collection device of this invention and yet permit the adaptation thereof to a particular application or user preference without departure from such basic design concept(s). As shown in figure 1, and discussed herein, one means for imparting such versatility can be achieved with a universal closure means (114) design which lends itself to user adaptation to a specific need or preference by simply interchanging the snap-in accessory of choice.

As illustrated herein in figure 8 comparable versatility in the sample collection device can be achieved with a universal sample collection tube design (812) of composite construction which lends itself to user adaptation to a specific need or preference by substitution of the conventional sample collection tube (112) of unitary design for a design with interchangeable snap-in accessory for the lower end (812c) of the sample collection tube (812). As shown in figure 8, the sample collection tube (812) can comprise a composite having an elongate barrel having an open end (812o) and a lower end (812c). The open end (812o) of the tube is substantially the same as the tube of unitary structure shown in figure 1 (e.g., external threads for engagement with a screw cap) and further includes means for modification of the lower end (812c) with any one of a number of snap-in accessory of the type described herein for the composite closure means (114, 214, 314) shown in figures 2, 3 & 4, respectively. In its simplest form, the composite sample collection device (810) of this invention can have a solid member as a snap-in accessory in the lower end (812c) thereof which can be replaced with a functional accessory, as

appropriate. More specifically, the lower end (812c) of the sample collection tube (812) illustrated in figure 8 is provided with a detente (817) formed within the barrel of the tube at the end thereof. This detente (817) can include a snap-in accessory with a fitting (815) designed for mating with a fixture as shown in figure 4B or a syringe such as is shown in figure 9. In each instance the choice of snap-in accessory can tailor the utility of the sample collection device to the particular needs and environment contemplated for its use.

In the embodiment of this invention illustrated in figure 9, the sample collection device (910) of this invention is provided with a closure means (914) of composite construction, which includes a fitting (918) adapted for mating with a syringe (950). Once the syringe (950) has been mated with the fitting (918) of the device, the contents of the syringe can be injected into the sample collection tube (912) through the closure means, by the syringe. As noted and once again emphasized, this fitting can be designed for mating with anyone of a number of a complimentary devices and/or accessories which permit access to the sample without removal of the closure means (914) or piercing of the sample collection device.

In those instances where the physical integrity of the sample collection device is not of concern, the sample can be accessed from within the sample collection tube by piercing the tube with a cannula and syringe combination. More specifically, the syringe used in the embodiments of this invention, once equipped with a cannula can easily puncture the tube or be inserted through the vent in the closure means to withdraw fluid from within the sample collection tube. In this latter embodiment of the invention, the

foam that is entrained with the webbing of the closure means functions much in the same way as septum of a vial, by permitting insertion of the cannula into the tube and yet effectively re-sealing the tube at the time the cannula is withdrawn.

In the configuration shown in figure 10, a Vacutainer-type syringe is placed in proximate relation to the close end of the sample collection tube and upon puncture of the tube effects withdrawal of sample from within the sample collection tube. More specifically, once the sample has been recovered from the absorbent medium, it can, thereafter be accessed from the sample collection tube (1012) by simply puncturing the lower end (1012c) of the tube with a cannula (1026) attached to a syringe (1050) and an aliquot of the sample withdrawn through the cannula into a syringe. In the embodiment of the syringe illustrated in figure 10, the barrel (1051) of syringe (1050) is under a negative pressure thereby effecting withdrawal of the sample. As an aliquot of the sample is withdrawn from the sample collection tube (1012), the tube may deform thus permitting an uninterrupted flow of sample into the syringe (1050) or air may enter through the vent (1011).

Alternative methods for accessing an aliquot of the sample from the sample collection tube, as shown in figure 11, include the provision of a preferably grooved needle (1126) integral with a test icon (1160) which houses an analyte sensitive element. In this embodiment of the invention illustrated in figure 11, a skirted tube of the design shown in figure 5, is placed in incipient mating relationship using alignment registration means (1175) of a test device. As the sample collection device (1110) and the test icon (1160) are each mated to the other, the grooved needle (1126) in the test icon punctures the lower end (1112c) of

the sample collection tube. An aliquot of the sample is thereby accessed and can be applied to the analyte sensitive element by simply squeezing the sample collection tube (1112) so as to cause the sample to flow down the needle grooves (not shown) and thereby initiate an analyte manifesting reaction within the analyte sensitive element in the test icon.

In yet another alternative embodiment of the invention shown in figure 12, the interaction of the constituents of the sample with analyte manifesting reactants can be accomplished entirely within the sample collection tube (1212), without removal of the closure means (1214) from the sample collection device (1210), by initially coating such reactants (1280) on the interior sidewall of the tube at the time of assembly and thereafter drying such reactants on the tube wall. It is also understood that the constituents in the sample may be measurable due to some intrinsic property, or alternatively, are manifest once having been combined with another substance which is present in the collection tube (1212) and/or added to the collection tube. More specifically, chemical substances (1280) can be coated on the interior of the collection tube (1212) and freeze dried. Upon introduction of the sample absorbent medium into the tube and the recovery of the fluid absorbed thereof by squeezing the sidewalls thereof in the direction indicated by the arrows, the chemicals are reconstituted and interact with the analyte of interest in the sample to produce a discernible change therein which is indicative of the analyte of interest. Alternatively, the chemicals can be present as a encapsulant (e.g., frangible microspheres) on the interior of the collection tube (1212). Thus, upon squeezing of the sidewalls of the tube, incident to recovery of the sample from the sample

absorbent medium, these microspheres (1280) are ruptured and the chemical agents contained therein are released and interact with one or more constituents in the sample to produce a detectable species that is indicative of the presence of the analyte in the sample.

Thus, subsequent to collection and upon expressing the sample from the sample absorbent medium (1216) within the tube (1212), the reactants are reconstituted by the sample and thereupon interact with the constituents of the sample so as to produce a discernible change within the sample collection tube (1212) that is indicative of the analyte of interest. This discernible change within the tube (1212) can include the formation of a distinctive color, increase in the turbidity in the fluid phase of the sample, formation of bubbles, formation of a precipitate, and/or any combination thereof.

Similarly, chemical agents can be entrained within the sample absorbent medium and not released unless and until the appropriate sequence in the analytical process is obtained. Obviously, where the sample is a biological fluid such as saliva, the use of chemical reagents in the tube and/or in conjunction with the sample absorbent medium must be approached with caution.

In the contemplated use and operation of the device of this invention, the sample is obtained by contact, (or immersion), of a sample absorbent medium with a source of a fluid suspected of containing an analyte of interest. In the context of analysis of waste water for a toxic substance (e.g., heavy metals, organic, etc.), a representative sample of the waste water is obtained and the sample absorbent medium simply immersed within the sample. The amount of the sample that need be absorbed to perform the desired

analysis is determined ultimately by the analytical protocol, and it is assumed this immersion procedure will supply more than adequate sample for the intended analysis.

Alternatively, where the device of this invention is to be used to collect a biological fluid sample (e.g., saliva) through contact of the sample absorbent medium with a sample donor, the contact must be of sufficient duration to allow for absorption of a representative sample and, preferably, be obtained under "normal" conditions (as compared to a saliva sample that is through the use of flavored element - a "stimulated" sample).

In the context of constituent analysis of saliva, with device of the design of figure 1, the sample absorbent medium of the device (110) of this invention can be readily adapted to the age of the donor (infants, toddlers, adults) and otherwise have varying porosity to make it more or less absorbent. Alternatively, this device (110) can be used with the other traditional biological fluids, (e.g., urine, whole blood, serum, etc.) and its design may thus vary accordingly. In each instance, the sample is obtained by first removal of the sample collection medium (116) from its secure environment within the collection tube (112), the sample collected as above described and the sample collection medium (116) sealed within the collection tube. Assuming that an adequate (by volume) sample has been obtained, it can thereafter be expressed by anyone of a number of techniques, depending upon the configuration of the device (110) of this invention, and once dispensed, subject to constituent analysis.

Again, depending upon the specific configuration of device of this invention, the collection of a representative sample of fluid is accomplished with relative ease and security. Although not

generally recommended when dealing with samples containing a toxic and/or infectious agent, the closure means obviously can be removed from the device to permit access to the sample with the sample collection tube, and an analyte sensitive element and/or chemicals can be added into the sample collection tube and allowed to interact with the recovered sample. This method of analysis is generally undesirable since it needlessly exposes the clinician and the environment to the used sample absorbent medium and the contents of the sample collection tube.

Where the sample is, however, suspected of containing infectious organisms, the preferred embodiment of the device selected will insure that once the sample has been obtained, it is retained within the secure environment of the collection tube and thereafter only supplied for analysis in a manner that prevents contamination of the ambient environment and those persons that must have access thereto for purposes of analysis.

Where the device of this invention does not afford access to the sample via a dispensing orifice integral with the device, or other means, the sample is generally obtained by first expressing the sample from the sample absorbent foam medium into a reservoir at the lower end of the sample collection tube, and then removing the closure means from the opening of the sample collection tube of the collection device, (which also results in the sample absorbent medium being withdrawn from the collection tube). An aliquot of fluid sample can thereafter be withdrawn from the sample collection tube with a pipette, or the sample simply transferred to another vessel for analysis, by pouring the sample from the tube into the test vessel. After at least some of the sample been removed from the tube, the sample absorbent medium and the closure

means are re-united with the sample collection tube and the tube sealed with the closure means.

The flexible sidewall design of the collection tube permits the dispensing of the sample from the sample absorbent foam medium by compressing the foam within the tube, where it collects in the reservoir in the lower end of the tube. During this process of sample collection, the volume of air confined within the tube is preferably displaced to allow for ease of compression of the sample collection tube and the squeezing of sample absorbent foam medium within the tube to be readily and most efficiently collection compressed. Where such confined air cannot be safely vented and, thereafter, the tube caused to re-expand, the sample collection process is inefficient, requires substantial pressure to squeeze the tube and express the sample, can cause potential damage to the tube and to the closure means and generally recovers less sample from the sample absorbent medium. The provision of a vent in the closure means dramatically improves the sample dispensing process without compromising the sealing of the device or requiring excessive squeezing of the collection tube, thus, minimizing the potentiality for damage to the collection device during the sample dispensing process.

As is apparent from the above, the collection of the sample within the device of this invention is only the beginning of the process for the determination of the presence of the analyte of interest, and, in some instances, the amount thereof. In order to accomplish such analysis, an aliquot of sample is contacted with an analyte sensitive element that is specific for the manifestation of the presence of the analyte of interest. In its simplest form, the analyte sensitive element can be one or more chemicals that are

reactive with the analyte interest, or, alternatively, an elaborate chemistry system. In each instance the analyte sensitive element can be contacted directly with the sample by the placement thereof into the collection tube, or an aliquot of sample dispensed from the sample collection tube and reacted with the analyte sensitive element in a test environment that is independent of the collection device of this invention. In the simplest embodiment of this invention, an aliquot of sample can be removed from the sample collection tube through the use of a pipette. As noted above, the preferred sample handling routine involves the use of one or more of the snap-in accessories to modify the closure means or the sample collection tube to enable dispensing of a recovered sample without removal of the closure means and the sample absorbent medium from the sample collection tube.

Typically, the sample recovered with the device of this invention can be subjected to analysis by one or more test protocols for determination of the presence and/or amount of the constituents of interest. In the performance of such analysis, a test kit (1300) of the type in the illustrated in figure 13 is provided which generally includes the sample collection device (1310) and all of the accessories (e.g., unit packages of reagents) (1380) and reagent system (1360) needed to complete the desired analysis. The manner in which such components are arranged and presented is often critical to proper and consistent test results, particularly when such test is to be performed by relatively unskilled personnel and at a location remote from a clinical laboratory. Accordingly, this invention includes, as illustrated in figure 14, a test kit package (1400) which provides a series of recesses (1490) and instructions for the package for arranging the

kit components in a "work station" format to insure proper sample and reagent utilization and consistent test results.

The examples which follow further define, describe and illustrate the various embodiments of this invention. Parts and percentages appearing in such examples are by weight unless otherwise indicated. Apparatus and equipment used in the fabrication and evaluation of the sample collection of this invention are standard unless otherwise indicated.

1. Fabrication of Sample Collector - A sample collection tube is initially obtained from East Coast Plastics, Inc., Ft. Lauderdale, Florida. This tube has a flexible sidewall, is substantially transparent, lower on one end and open on the opposite end. This sample collection tube is approximately 3 inches in length and has an inside diameter of 0.5 inches. The open end thereof is provided with external threads for sealing engagement with a closure means (screw cap) of the type shown in figure 3.

A sample absorbent medium is prepared by molding a hydrophilic polyurethane foam compound (HYPOL FHP 2002, available from W. R. Grace, Boca Raton, FL), utilizing the tube of the collection device as a form. More specifically, a foam medium is fabricated by injection of a foam compound through the open end of the closure means into the collection tube, allowing the foam to expand within the tube into and surrounding the webbing of the closure means. As the foam cures it shrinks within the tube, thereby providing a space between the sample absorbent foam and the sidewall of the tube. The foam also shrinks in the long dimension thereby providing a reservoir in the end the tube for the collection of sample. The shrinkage of the foam does not affect its attachment

to the webbing of the closure means, where it remains anchored. A snap-in accessory is thereafter inserted into the top of the closure means to complete the device.

The HYPOL foam compound selected for this application is formulated to shrink approximately 40%, thereby permitting the absorbent medium to be easily withdrawn and reinserted into the tube incident to the sample collection process. Since the absorbent medium is integral with the closure means, it does not require any further processing to secure it. Once the foam has sufficient green strength, the cap and the foam medium can be removed from the tube and inserted into the saliva donor's mouth and allowed to absorb saliva.

2. Collection of the Sample - After the device has been fabricated in the above manner, it can be used to obtain a fluid sample for preservation and/or analysis. Initially, the closure means and sample absorbent foam is removed from the device by simply unscrewing the closure means from the collection tube. The sample collection process can simply involve the immersion of the foam into a fluid sample or by the contact of this foam with a sample donor. In the context of saliva collection, this foam medium is placed in the donor's mouth and allowed to remain in contact with salivary secretions for an abbreviated period of time (generally 3 to 5 minutes). It is important to emphasize that the salivary secretion is collected under normal conditions and that the donor's salivary glands are not stimulated by prior contact with food or other artificial means. After sufficient saliva (at least 75 to 100 micro liters) has been absorbed by the fluid absorbent foam, the foam is removed from the donor's mouth, placed in the collection tube and the tube sealed as before with the

closure means. The sample can thereafter be recovered by simply squeezing the flexible sidewall of the collection tube. The physical properties of the recovered sample closely approximate those of water (saline) and thus further analysis thereof can be accomplished without any additional sample preparation or treatment.

3. Sample Analysis - Once the sample has been collected and dispensed in the manner described above, it can be subject to analysis and testing by the contacting an aliquot thereof with one or more components of a diagnostic test kit, e.g., immunoreagents specific for interaction with one or more constituents of the sample. Typically, these additional kit components include an analyte sensitive element (test strip) and one of more additional reagents, depending upon the assay format and analyte of interest.

In a diagnostic test for determination of the presence of antibodies indicative of the AIDS virus (HIV), the analyte sensitive element comprises an HIV specific binding protein immobilized within a membrane that is supported in a housing. The HIV specific analyte sensitive element is available commercially, for investigational use, from Chembio Corp., Medford, N.Y.

In the Chembio diagnostic test for the analysis of saliva for antibodies to the HIV virus, the analyte sensitive element is fabricated form a nitrocellulose membrane backbone support that is spotted with the specific antigen fragments (i.e., p120, gp40) that are bound to the membrane after the membrane has been prepared to accept the antigen mixture. The antigen lined membrane is thereafter is immersed in a solution containing a wetting agent and a protein (BSA or Casein) to block the unreactive sites. The resultant HIV specific membrane is then dried as above. The dried

membrane is mounted in a holder which contains a molded-in well and absorbent pad to for absorption of excess sample.

In a diagnostic test for determination of the presence of antigen indicative of infectious Hepatitis (HBsAG), the analyte sensitive element comprises a linear test strip having a series of zones, each specific for performance of a discrete function. The analyte sensitive element is available commercially, for investigational use, from Bionike, San Francisco, California.

The analyte sensitive element comprises a sample pad which is integrated with and/or in fluid communication with a test strip (nitro cellulose membrane). The sample collection pad is of sufficient void volume to accommodate adequate sample to perform the contemplated assay. The functional areas of the membrane include a reagent zone within which is deposited (and lyophilized) an unbound (mobile) gold labeled antibody conjugate specific for interaction with the analyte of interest (HBsAG). Thus, upon application of the sample to the analyte sensitive element, the sample reconstitutes the gold labeled conjugate and thereby provides a medium for the interaction between the analyte and the conjugate, so as to form an immunocomplex. As the sample is absorbed by the test element, it causes this immunocomplex, and any excess (unreacted) conjugate, to pass along the fluid pathway within the test element where it comes in contact with an immobilized binding substance (e.g., antibody) specific for interacting with and which includes one or more delimited areas having an immobilized binding material specific for the interaction with a constituent of a biological fluid sample or a reaction product which includes a constituent of the biological fluid sample. The analyte sensitive element is preferably mounted in a

fixture with other accessory components to assist in the distribution and flow of the biological fluid sample within the analyte sensitive element. The format of the analyte sensitive element suitable for use in this invention can accommodate amounts of fluids generally in excess of that required to perform the assay so as to permit its use in the home health case (self-testing) environments.

Claims

What is claimed is:

1. A sample collection, dispensing and retention device comprising:

a sample collection tube having an open end and a lower end;

a closure means for selective sealing engagement with the open end of the sample collection tube;

webbing fixedly disposed within the closure means; and

a porous sample absorbent medium for contact with and adsorption of a fluid sample and having a geometry to removably dispose said medium within the sample collection tube, said medium being formed around and internally retaining the webbing to fixedly attach a portion of said medium within said closure means.

2. The device of claim 1 in which the porous sample absorbent medium is a hydrophilic cross linked polyurethane foam.

3. The device of claim 2 in which the medium being formed around and internally retaining the webbing is accomplished by foaming the polyurethane in place around the webbing.

4. The device of claim 1 which further comprises a vent in the closure means.

5. The device of claim 1 which further comprises an internal screw thread for engagement with a complimentary thread on the open end of the sample collection tube.

6. The device of claim 1 in which a closed end of the closure means is defined by a snap-in accessory.

7. The device of claim 6 wherein the snap-in accessory is configured for dispensing a sample from the collection tube.

8. The device of claim 6 wherein the snap-in accessory includes a fitting that is configured for mating with a fixture

including an analyte sensitive element.

9. The device of claim 6 wherein the snap-in accessory includes a fitting that is configured for mating with a syringe.

10. The device of claim 1 in which the lower end of the sample collection tube is closed.

11. The device of claim 1 in which the sample collection tube is comprised of a resilient elastomeric material such that a sample can be expressed from the sample absorbent medium by squeezing the sample collection tube.

12. The device of claim 11 which further comprises a reservoir at the lower end of the sample collection tube which allows for the segregation of the sample once it has been expressed from the fluid absorbent medium into the reservoir of the sample collection tube.

13. The device of claim 1 in which the lower end of the sample collection tube is defined by a snap-in accessory.

14. The device of claim 1 wherein the lower end of the collection tube includes a skirt.

15. The device of claim 14 wherein the skirt includes a detente to capture a snap-in accessory.

16. The device of claim 14 which further comprises a test icon in cooperative relationship therewith.

17. The device of claim 1 wherein the lower end of the collection tube includes pipette tip.

18. The device of claim 1 wherein the lower end of the collection tube includes a dispensing tip having an internal pressure activated valve.

19. The device of claim 13 wherein the snap-in accessory includes a fitting that is configured for mating with a fixture

including an analyte sensitive element.

20. The device of claim 13 wherein the snap-in accessory is configured for dispensing a sample from the collection device.

21. The device of claim 13 wherein the snap-in accessory includes a fitting that is configured for mating with a syringe.

22. The device of claim 1 wherein the lower end is configured to fit snugly within and be punctured by a cannula of a Vacutainer-like syringe.

23. The device of claim 1 wherein a sidewall of the collection tube includes a reagent coating specific for interaction with at least one constituent in a sample.

24. The device of claim 1 which further comprises a test kit.

25. The device of claim 24 in which the test kit is configured as a workstation.

26. The device of claim 24 in which the test kit includes a reagent specific for interaction with at least one constituent in a sample.

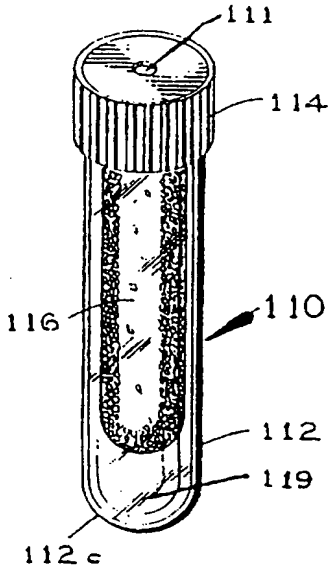


FIG. 1

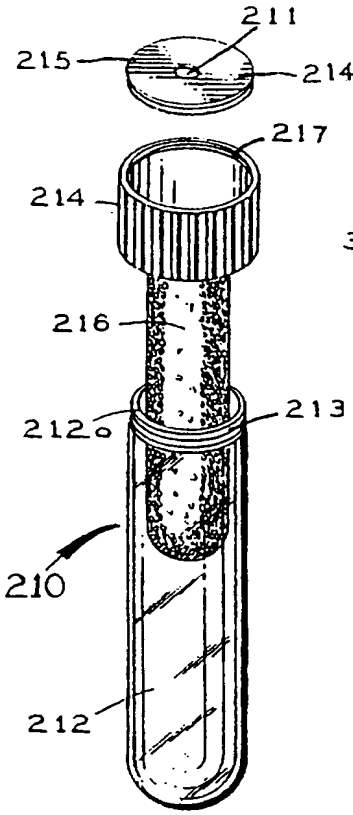


FIG. 2

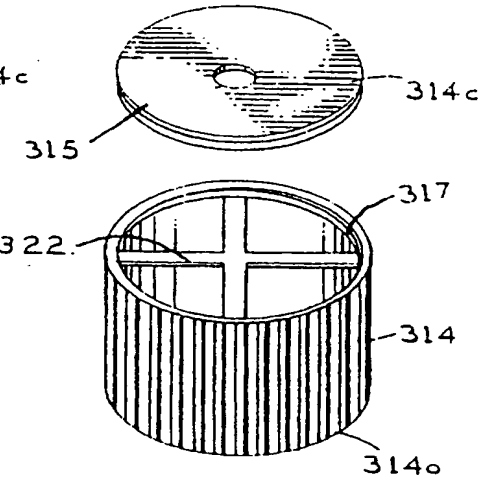


FIG. 3A

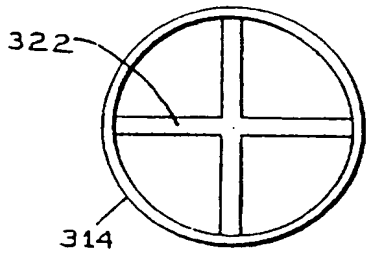


FIG. 3B

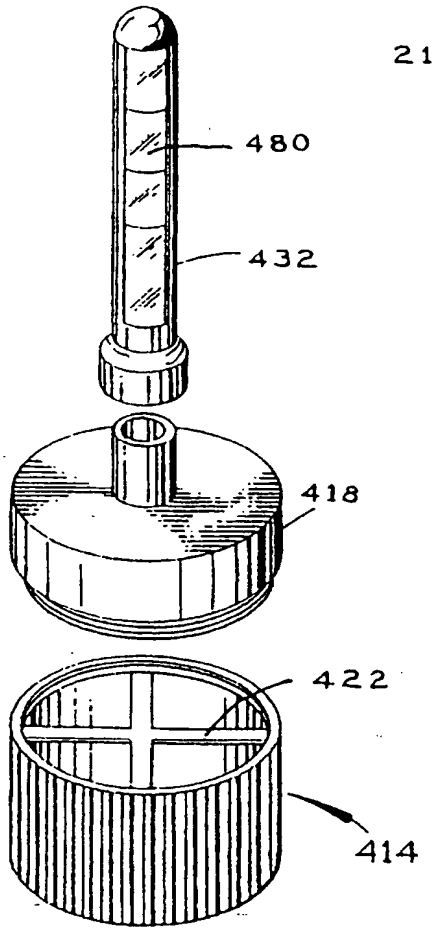


FIG. 4B

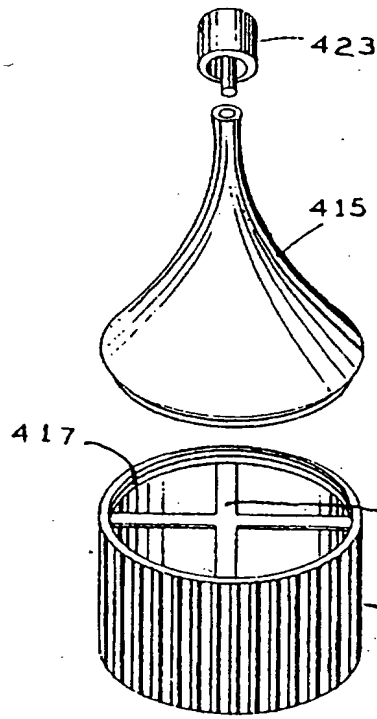


FIG. 4A

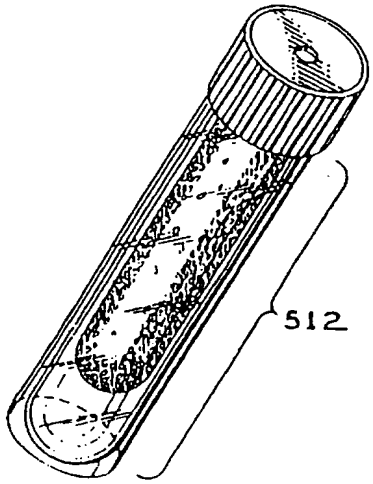


FIG. 5

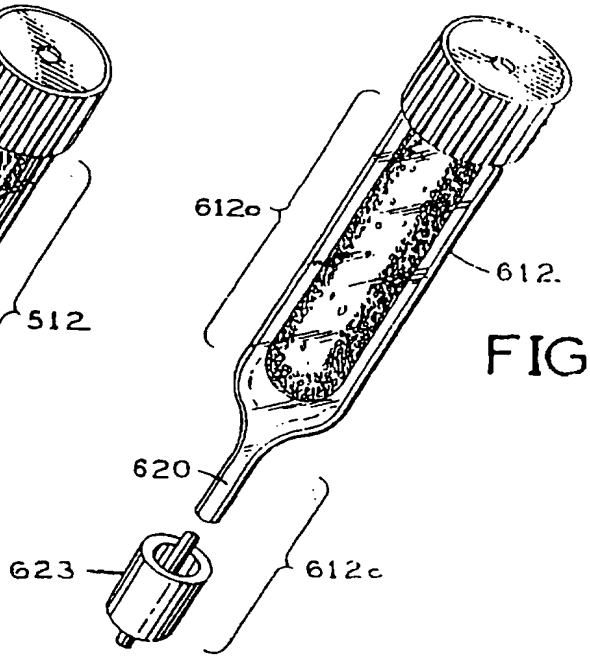


FIG. 6A

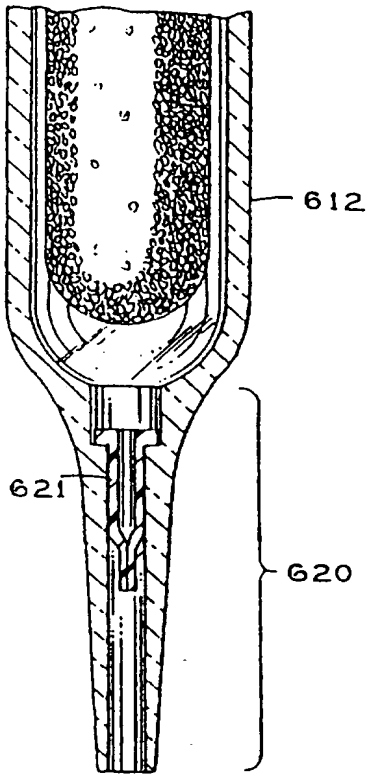


FIG. 6B

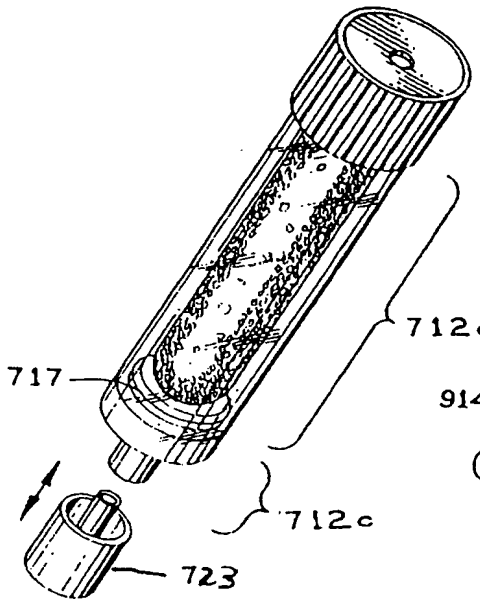
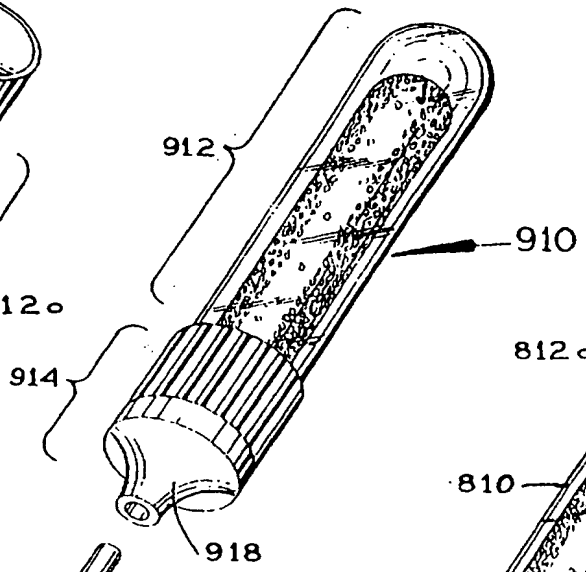


FIG. 7



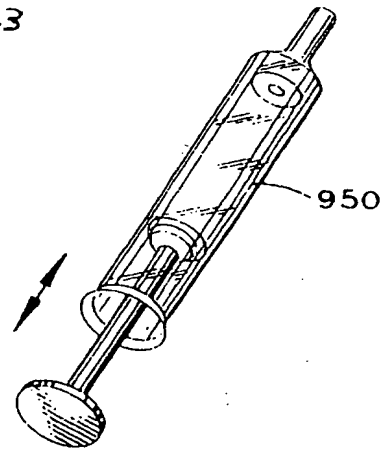


FIG. 9

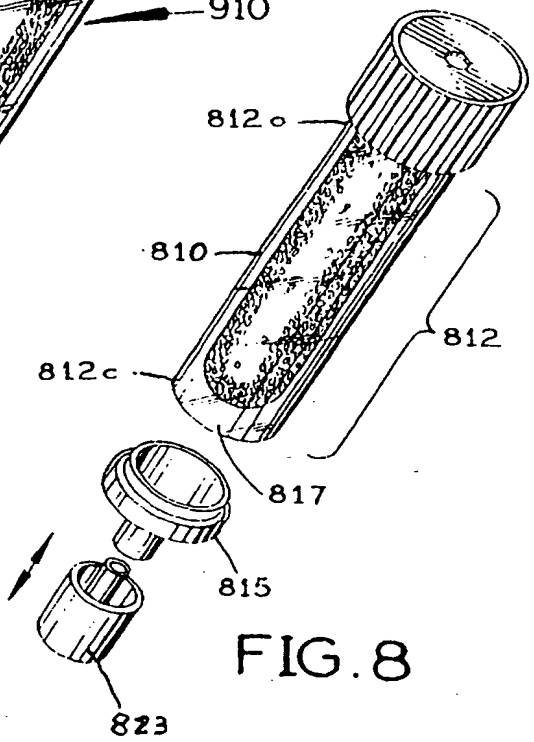


FIG. 8

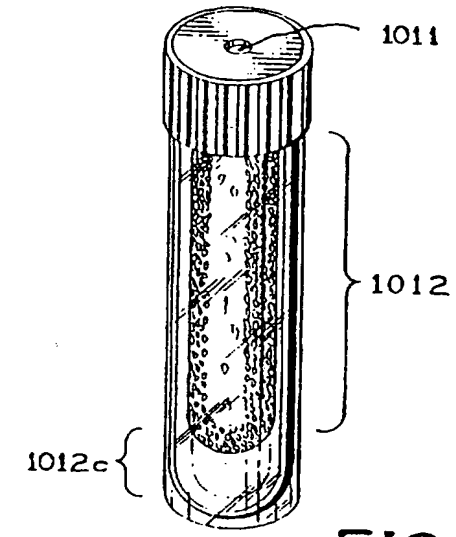
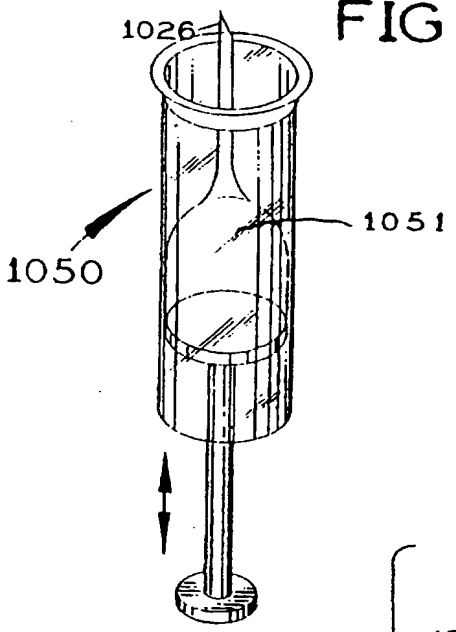


FIG. 10



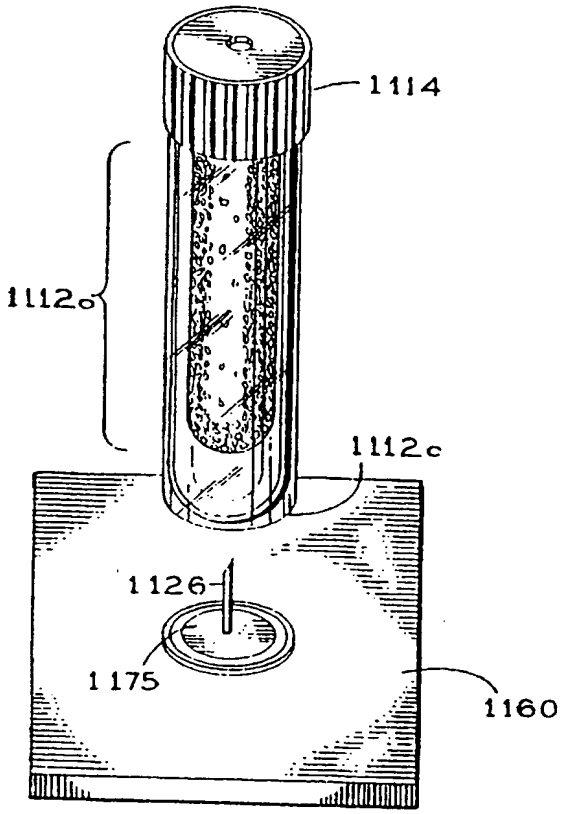


FIG. 11

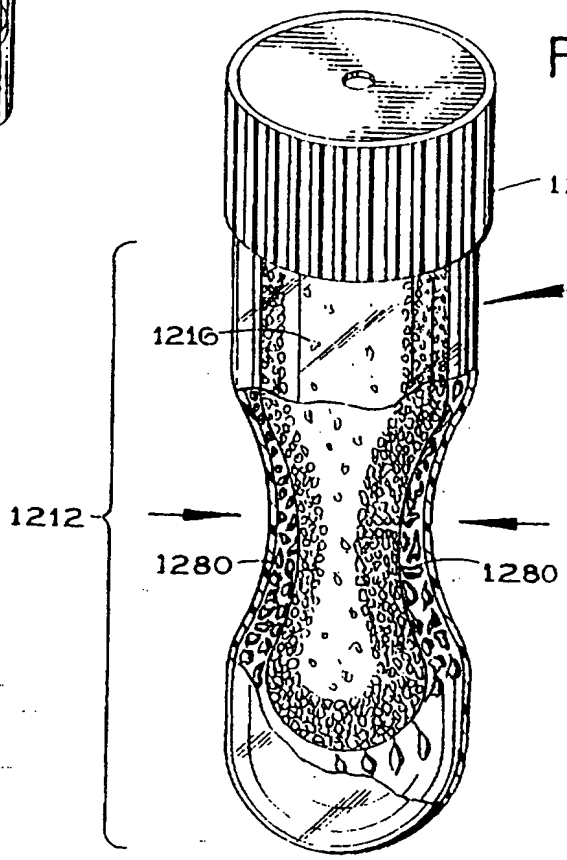


FIG. 12

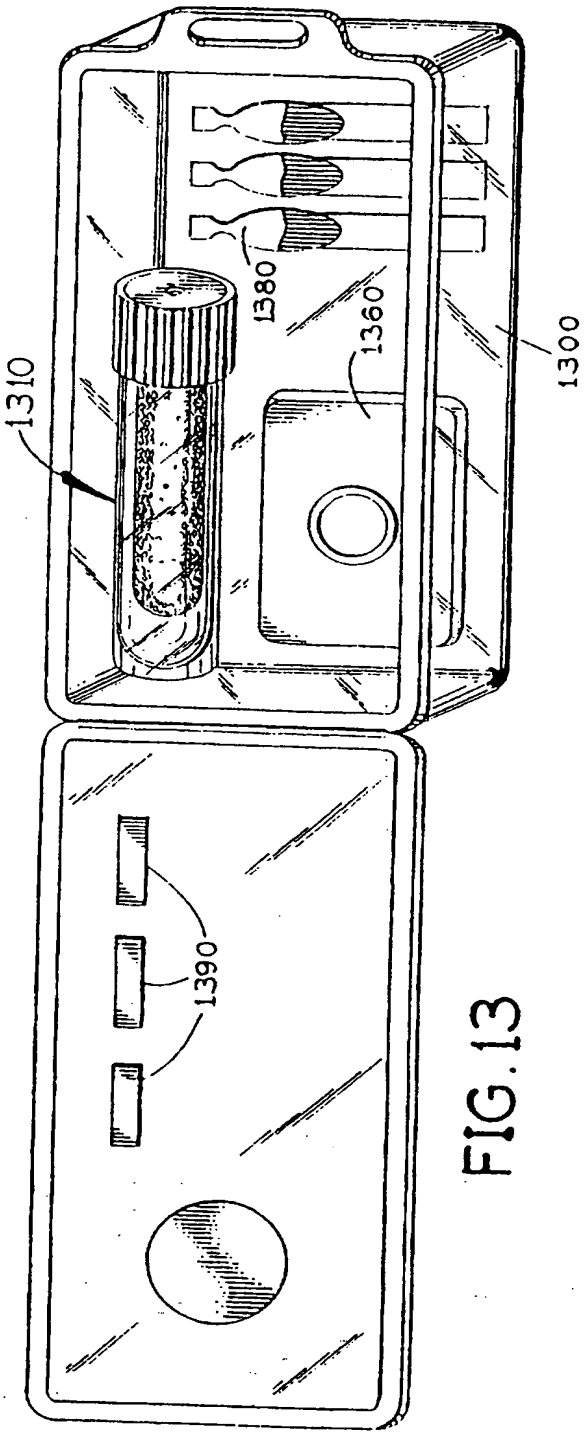


FIG. 13

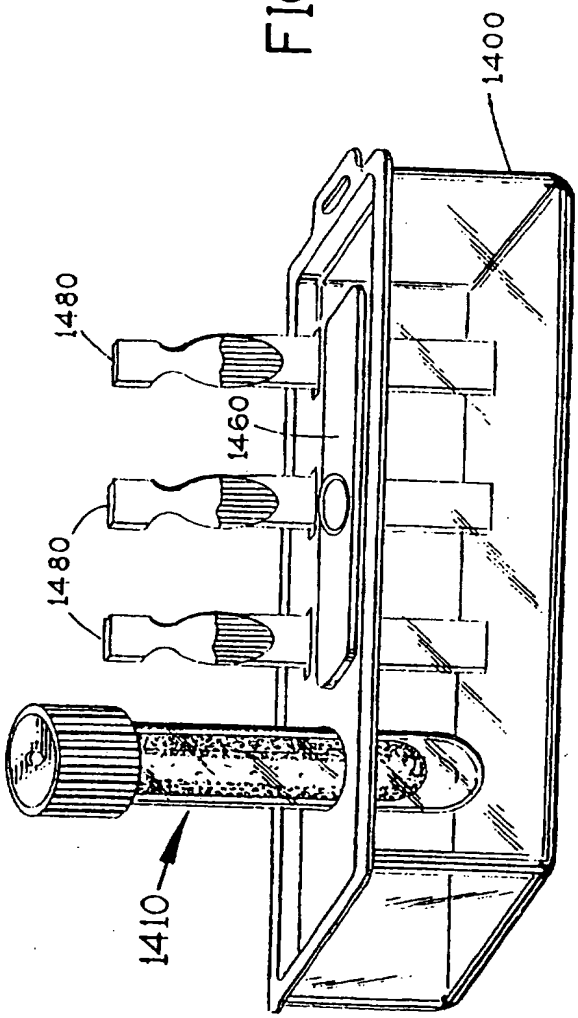


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12880

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :B01L 3/14
US CL :422/102
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/56, 58, 68.1, 84, 85, 86, 88, 101, 102, 104

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 5,352,410 A (HANSEN et al) 04 October 1994, see entire document.	1 ------ 2-26
Y	US 5,427,739 A (MESEROL et al) 27 June 1995, see entire document.	1-26
Y	US 5,103,836 A (GOLDSTEIN et al) 14 April 1992, see entire document.	1-26
Y	US 4,873,193 A (JENSEN et al) 10 October 1989, see entire document.	1-26
Y	US 4,635,488 A (KREMER) 13 January 1987, see entire document.	1-26
Y	EPA 0,383,262 A2 (YAMAZAKI et al) 13 February 1990,	1-26

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 SEPTEMBER 1997	Date of mailing of the international search report 15 OCT 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer HAROLD Y. PYON Telephone No. (703) 308-0651

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12880

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,160,704 A (SCHLUTER) 03 November 1992, see entire document.	1-26
Y	US 4,878,597 A (HAAST) 07 November 1989, see entire document.	1-26

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